

**Amendments to the Claims:**

This listing of claims will replace all prior versions, and listings, of claims in the application.

These amendments introduce no new matter and support for the amendment is replete throughout the specification and claims as originally filed. These amendments are made without prejudice and are not to be construed as abandonment of the previously claimed subject matter, or agreement with any objection or rejection of record.

**Listing of Claims:**

1. (Currently Amended) A method of detecting a component of interest, the method comprising:
  - (a) providing one or more nanowires, which nanowires comprise one or more functional group comprising a hairpin oligonucleotide, which functional group undergoes a change in charge in the presence of the component of interest;
  - (b) contacting the one or more nanowires with a solution comprising the component of interest; which component produces the change in charge in the functional groups, which change in charge results in a detectable signal; and,
  - (c) detecting the signal, thereby detecting the component of interest.
2. (Original) The method of claim 1, wherein the component of interest comprises an enzyme, a nucleic acid, or a protein.
3. (Withdrawn) The method of claim 2, wherein the enzyme comprises a protease, a kinase, a phosphatase, a protease, a polymerase, a ligase, or a transferase.
4. (Withdrawn) The method of claim 1, wherein the component of interest comprises an enzyme and the functional group comprises an enzymatic substrate.
5. (Withdrawn) The method of claim 4, wherein the enzymatic substrate comprises a protein, a peptide, or an oligonucleotide.

6. (Withdrawn) The method of claim 4, the method further comprising determining an initial rate for an enzymatic activity of the enzyme.

7. (Cancelled)

8. (Currently Amended) The method of claim [[7]] 1, wherein the hairpin comprises a first end, a second end, and a central portion, wherein the first end and the second end are complementary to each other and the central portion is complementary to the component of interest, and wherein the first end comprises a charge moiety that is proximal to the nanowires; wherein binding the component of interest to the central portion of the hairpin oligonucleotide unfolds the hairpin, thereby moving the charge moiety away from the nanowires, producing the change in charge.

9. (Original) The method of claim 8, wherein the charge moiety comprises a latex bead comprising a carboxylate or amine surface, a nucleic acid, a highly charged polypeptide, a charged polymer, one or more negatively charged nucleotides, or a metal nanocrystal.

10-15. (Cancelled)

16. (Original) A method of detecting glucose, the method comprising:

(a) providing one or more nanowires that comprise glucose oxidase immobilized thereon or proximal thereto;

(b) contacting the nanowires with a test solution; wherein any glucose present in the test solution is oxidized by the glucose oxidase resulting in a change in pH of the test solution, wherein the change in pH produces a signal in the nanowires; and,

(c) detecting the signal, thereby detecting the glucose in the test solution.

17-81. (Cancelled)

82. (New) The method of claim 1, wherein the hairpin oligonucleotide has a first end, a second end and a central portion, wherein the central portion binds the component of interest.

83. (New) The method of claim 82, wherein the component of interest is a nucleic acid and wherein the central portion is complementary to the nucleic acid.

84. (New) The method of claim 1, wherein the hairpin oligonucleotide unfolds to produce the change in charge.

85. (New) The method of claim 1, wherein the one or more nanowires comprise a nanowire array.

86. (New) The method of claim 1, wherein the one or more nanowires are positioned in one or more microwells or within a microfluidic device.

87. (New) The method of claim 1, wherein the component of interest comprises a cellular component.

88. (New) The method of claim 1, wherein the change in charge comprises a redistribution of charge.

89. (New) The method of claim 1, wherein the solution comprises one or more cells, one or more cellular fragments, a tissue sample, a cell lysate, or a blood sample.

90. (New) The method of claim 16, wherein the test solution comprises one or more cells, one or more cellular fragments, a tissue sample, a cell lysate, or a blood sample.

91. (New) The method of claim 16, wherein the one or more nanowires are positioned in one or more microwells or within a microfluidic device.

92. (New) The method of claim 16, wherein the one or more nanowires comprise a nanowire array.

REMARKS/ARGUMENTS

**The Status of the Claims.**

Claims 1-6, 8-9, 16, and 81-92 are pending with entry of this amendment, claims 7, 10-15, and 17-81 being cancelled and claims 82-92 being added herein. Claim 1 is amended herein and new claims 82-92 are added. This amendment introduces no new matter and support for the amendments and additions is replete throughout the specification. This amendment is made without prejudice and is not to be construed as abandonment of the previously claimed subject matter or agreement with any objection or rejection of record.

With respect to amended claim 1, support for the amendment can be found throughout the specification. For example, see specification at page 33, paragraphs 120 and 121, and original claim 7 describing the use of hairpins in the nanosensors of the invention. Support for new claims 82-84 and 88 is found, e.g., on page 33, paragraphs 120 and 121, and original claim 8, describing hairpin oligonucleotides as functional groups. Support for new claims 85 and 92 is found, e.g., on page 21, paragraphs 84-85 describing arrays of nanowires. Support for new claims 86 and 91 is found, e.g., on page 24, paragraph 94, and page 25, paragraph 95, describing the positioning of nanowires into microwells and microfluidic systems. Support for new claims 87, 89, and 90 is found, e.g., on page 41, paragraph 143, and page 36, paragraph 132, describing types of solutions that are optionally tested with the sensors of the application.

Applicants submit that no new matter has been added to the application by way of the above Amendment. Accordingly, entry of the Amendment is respectfully requested.

**The Election/Restriction Requirement.**

Pursuant to a restriction requirement made final, Applicants cancel claims 10-15 and claims 17-81 with entry of this amendment. Please note, however, that Applicants reserve the right to file subsequent applications claiming the canceled subject matter and the claim cancellations should not be construed as abandonment or agreement with the Examiner's position in the Office Action.

**The Information Disclosure Statement.**

Applicants note with appreciation the Examiner's thorough consideration of the references cited in the Information Disclosure Statement (Form 1449) submitted on March 10, 2004.

**35 U.S.C. §102.**

Claim 1 was rejected under 35 U.S.C. §102(b) as allegedly anticipated by Cui et al., Science 293: 1289-1292 (2001). In order for a reference to anticipate an invention, the reference must teach each every element of the claimed invention.

To expedite prosecution, Claim 1 is amended herein and is believed to be in condition for allowance. This amendment is made without prejudice and is not to be construed as abandonment of the previously claimed subject matter or agreement with any objection or rejection of record. However, rejection of the amended claim under Cui is moot because Cui, as acknowledged by the Examiner, does not teach anything regarding hairpin oligonucleotides. Applicants therefore respectfully request that the rejection be withdrawn.

**35 U.S.C. §103(a) – Cui in view of Bashir or Lim**

Claims 1 and 2 were rejected under 35 U.S.C. §103(a) as allegedly obvious in light of Cui in view of Bashir, US Patent No. 6,716,620. Claims 1 and 2 were also rejected under 35 U.S.C. §103(a) as allegedly obvious in light of Cui in view of Lim, US Patent Appl. Pub. No. 2003/0102510.

Three requirements must be met for a *prima facie* case of obviousness. First, the prior art reference must teach all of the limitations of the claims. M.P.E.P. § 2143.03. Second, there must be a motivation to modify the reference or combine the teachings to produce the claimed invention. M.P.E.P. § 2143.01. Third, a reasonable expectation of success is required. M.P.E.P. § 2143.02. The teaching or suggestion to combine and the expectation of success must be both found in the prior art and not based on Applicants' disclosure. M.P.E.P. §2143.

These two rejections are moot in light of the amended claims as they do not teach every element of the claimed invention. As acknowledged on page 8 of the Office Action, neither Cui, Bashir, or Lim teach a hairpin oligonucleotide. The above rejections bases on obviousness cannot be maintained without every element of the claimed invention. Applicants therefore respectfully request that these rejections be withdrawn.

**35 U.S.C. §103(a) – Cui in view of Bashir or Lim, and Zhao**

Claims 1, 2, and 7 were rejected under 35 U.S.C. §103(a) as allegedly obvious in light of Cui in view of Bashir and Lim and further in view of Zhao, *Nucleic Acids Research* 29(4):955-959 (2001). The Action states that Cui teaches the use of nanowires to detect biological and chemical species, but does not specifically address the detection of nucleic acids. The action relies on either Lim or Bashir to teach the nucleic acid element of the claim and Zhao to teach the hairpin element of the claim.

Specifically, a *prima facie* case of obviousness requires that the combination of the cited art, taken with the general knowledge in the field, must provide all of the elements of the claimed invention. When a rejection depends on a combination of prior art references, there must be some teaching, suggestion or motivation to combine the references. In re Geiger, 815 USPQ2s 1276, 1278 (Fed. Cir. 1987). Moreover, to support an obviousness rejection the cited references must additionally provide a reasonable expectation of success. In re Vaeck, 20 USPQ2d 1438 (Fed. Cir. 1991), citing In re Dow Chemical Co., 5 USPQ2d 1529, 1531 (Fed. Cir. 1988).

The Examiner States that, “ Zhao teaches a method for immobilization of oligonucleotides useful in hybridization assays, wherein the capture probes have hairpin structures with multiple attachment sites.” Even if the Examiner’s assessment of what Zhao teaches is correct, this teaching is not what the present invention claims. The reference does not teach a hairpin oligonucleotide functional group that changes charge upon contact with a component of interest. Therefore the cited references do not teach every element of the claims and the rejection should be withdrawn.

Second, there must be a particular motivation for combining the references. No *particular* motivation for combining Cui with either Lim or Bashir and then combining those with Zhao is offered in the rejection. The Examiner makes no case for motivation to combine other than to state that “one of ordinary skill in the art would have recognized the advantages of the multipoint surface attachment strategy with the hairpin oligonucleotide of Zhao and its usefulness in any detection format, such as those taught by Cui, Bshir and/or Lim.” Applicants do not dispute that such an implied rationale can, theoretically, form the basis for finding a motivation to combine. However, this “implied rationale” must still meet the requirements of *particularity*, i.e., the rejection must relate to the *particular* references and claim limitations at issue. This requirement for particularity in the rejection is the counterbalance to simply making a raw hindsight reconstruction argument, in which the Examiner simply restates a *benefit* provided by an Applicant’s invention (e.g., a new way to use hairpin nucleotides in hybridization assays on nanowires) as the *motivation* for the asserted combination. This type of rationale comprises improper hindsight reconstruction of the invention.

The requirement for particularity in the combination is in place to avoid this type of improper hindsight reconstruction. As set forth in the MPEP, “Obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching suggestion or motivation to do so found either explicitly or implicitly in the references themselves or in the knowledge generally available to one of ordinary skill in the art.” MPEP 2143.01. As the Courts have clearly stated, this means that the Patent Office “must explain why one of ordinary skill in the art would have been motivated to select references and to combine

them to render a claimed invention obvious.” Moreover, as the Court stated with respect to the type of evidence of motivation that must be presented by the Office, **“the need for specificity pervades this authority. ‘Particular findings must be made as to the reason the skilled artisan, with no knowledge of the claimed invention, would have selected these components for combination in the manner claimed.’”** In Re Lee 61 USPQ 1430 at 1433, (Fed Cir. 2002), *citations omitted*.

It is plain that the action confuses the concept of a *general* motivation with the required *specific* motivation to combine the references in question. There is nothing in Cui, Lim, Bashir, or Zhao that remotely suggests or motivates the particular combination of references at issue - at most, the Examiner’s allegation is that Cui teaches nanowires for detection of biological species, and that *general* methods of DNA detection are taught by Lim and Bashir, and that Zhao teaches a multi-point attachment strategy for hairpins. There is no teaching that hairpins *in particular* would be useful in the nanowire nucleic acid detection methods of the present invention. (Nor are the hairpin attachment methods used in Zhao appropriate for the use of hairpins as presently claimed).

Finally with regard to motivation to combine, the Examiner still has not stated *how* the combination of references is even to be achieved. The attachment method of the hairpin in Zhao does not show how such a hairpin functional group would produce a change in charge in the presence of the component of interest. Applicants question: how are the Zhao protocols to be applied to the nanowires of Cui to provide a biosensor as described in the present invention without reference to the present application itself? For the present invention to be achieved, reference must be made to the present application to introduce a hairpin that produces a change in charge in a nanowire detection system and the Examiner has shown no rational way that the combination of references can render the claimed invention obvious.

Third, the cited references must provide a reasonable expectation of success. The Examiner states that, “One of ordinary skill in the art would have a reasonable expectation of success in arriving at the invention as claimed because each of Cui, Bashir, Lim, and Zhao are directed to oligonucleotide-based hybridization assays.” Even if true, the fact that a group of references are directed to the same technology, does not mean that the elements of the references when combined will successfully work in a different manner, e.g., the manner claimed.

As discussed above, the hairpin attachment methods of Zhao use multiple sites in the hairpin loop to attach a hairpin oligonucleotide to a surface for use in hybridization assays. There is no indication in the references provided as to how such an attachment strategy would result in a change in charge as presently claimed. In fact, the multi-site loop attachment strategy would not work in the present invention where the loop nucleotides are typically used as a recognition site. Therefore, no expectation of success exists for the combination relied upon in the rejection.

In short, the combination of Cui and Zhao with either of Bashir or Lim completely fails to establish a case for obviousness. The combination of references does not provide each of the limitations of the claims; there is no *specific* motivation to make the combination of references, and no expectation of success for the attachment of a hairpin to a nanowire as in Zhao to work as a biosensor as described in the present invention. The rejection completely fails to state a case for obviousness and must be withdrawn.

**35 U.S.C. §103(a) – Cui in view of Brand**

Claim 16 was rejected under 35 U.S.C. §103(a) as allegedly obvious in light of Cui in view of Brand, *Appl. Microbiol Biotechnol* 36 (2): 167-72 (1991).

As discussed above, three requirements exist for a *prima facie* case of obviousness. In the subject rejection, no *particular* motivation for combining Cui and Brand is offered. As discussed in depth above, to avoid a hindsight reconstruction of the invention, the rejection must provide a *particular* finding as to why one of skill in the art would have been specifically motivated to combine these two references into the claimed invention.

There is nothing in Cui or Brand that remotely suggests or motivates the combination of references at issue—at most, the Examiner’s allegation is that Cui teaches semiconductor nanowires used as detectors for biological components and that Brand teaches a FET glucose sensor. There is no teaching or suggestion that the glucose sensor of Brand *in particular* would benefit from the Cui nanowire methods. In fact, the point of the article by Brand is to show that the bio-FETs in use for that article are sufficient, i.e., sensitive enough, for glucose detection. See, e.g., page 167, the introduction, where it states that the purpose of the article is show the practical application of biosensors. No need or particular motivation is shown or suggested for replacing the sensor used in Brand with a nanowire as used in Cui to provide a glucose nanosensor as claimed. One of the benefits of the claimed glucose biosensor is its sensitivity levels. In fact, not only is no particular need, motivation, or suggestion provided in the prior art to modify the sensors of Brand to use the nanowire FETS of Cui, the article itself points to the sufficiency of the macroscale detectors in use and thus teaches away from the need for such a modification.

As also previously noted, a final requirement of establishing a case for obviousness is that there must be an expectation for success for the combined references to work as the claimed invention. M.P.E.P. § 2143.02. The rejection is entirely non-specific, and does not *allege* how each and every limitation of the claims would be combined into a successful glucose detector without reference to the present application.